REMARKS

Status of the Claims.

Claims 1-29 are pending with entry of this amendment, claims 30-78 being canceled herein. Claims 12 and 26 are withdrawn from consideration. Claims 19 and 21 are amended herein to ensure that antecedent basis is clear. Support for the amendment is found at least in the original claims, especially the base claims, and generally throughout the specification. Therefore, these amendments introduce no new matter.

Election/Restriction.

Pursuant to a restriction requirement made final, Applicants cancel claims 30-78 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter, and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Information Disclosure Statement.

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statements (Form 1449) submitted on March 24, 2004 and August 5, 2004.

Specification.

The Examiner objected to the specification for containing an embedded hyperlink on page 81. As the specification has been amended to delete this hyperlink, Applicants respectfully request withdrawal of the objection.

35 U.S.C. §112, First Paragraph.

Claims 1-11, 13-25, and 27-29 were rejected under 35 U.S.C. §112, first paragraph, on the ground that the specification allegedly "does not . . . provide enablement for [the] genus of administering an inhibitor or administering a polypeptide that is other than the polypeptide of SEQ ID NO:2 or 6, nor for *in vivo* uses of the methods." Office Action, page 3. This rejection is respectfully traversed.

Of the pending claims, only claim 1 and claim 18 are independent. Claim 1 recites:

> A method of inhibiting agonist-induced down-regulation of a G protein-coupled receptor, the method comprising contacting cells comprising the G protein-coupled receptor with an effective amount of an inhibitor, wherein:
>
> the G protein-coupled receptor is one that specifically binds to a polypeptide having the amino acid sequence of GASP SEQ ID NO:2 (GASP1) or GASP SEQ ID NO:6 (GASP2);
>
> the inhibitor reduces specific binding of the G protein-coupled receptor to said polypeptide; and
>
> an effective amount is an amount sufficient to reduce agonist-induced down-regulation of the G protein-coupled receptor in the cells.

In this claim, the inhibitor is defined, generically, as an agent that "reduces specific binding of the G protein-coupled receptor to said polypeptide."

Claim 18 recites:

> A method of enhancing agonist-induced down-regulation of a G protein-coupled receptor, the method comprising contacting cells comprising the G protein-coupled receptor with an effective amount of a polypeptide that increases agonist-induced down-regulation of the G protein-coupled receptor, wherein:
>
> the G protein-coupled receptor is one that specifically binds to a polypeptide having the amino acid sequence of GASP SEQ ID NO:2 (GASP1) or GASP SEQ ID NO:6 (GASP2);

> the polypeptide comprises an amino acid sequence that has at least about 70% identity to GASP SEQ ID NO:2 (GASP1) or GASP SEQ ID NO:6 (GASP2) over a comparison window of at least 15 contiguous amino acids; and
>
> an effective amount is an amount sufficient to increase agonist-induced down-regulation of the G protein-coupled receptor in the cells.

In claim 18, the agent that enhances agonist-induced down-regulation is a polypeptide that is defined structurally, i.e., a polypeptide having an amino acid sequence that has at least about 70% identity to GASP1 or GASP2. This polypeptide is also defined functionally, namely, as one that "increases agonist-induced down-regulation of the G protein-coupled receptor." Accordingly, 18 reads on the use of a genus of polypeptides that enhance agonist-induced down-regulation.

The basis for the rejection is that these claims each relate to a genus of modulators of down-regulation, whereas the specification exemplifies one inhibitor of down-regulation (truncated GASP1) and two polypeptide enhancers of down-regulation (GASP1 and 2). Applicants respectfully point out that those of skill in art would readily appreciate, from the teachings of the specification, that truncated GASP2 would also inhibit down-regulation in a manner similar to truncated GASP1.

However, the Examiner takes the position that the "claims are, in essence, single means claims, because the claims encompass any composition having the recited activities whereas the instant specification only discloses . . . two . . . compositions known to the inventor." Office Action, page 6. In support of this contention, the Examiner cites *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). Applicants respectfully submit that the claims at issue in the present application are not single means claims and that the facts of the present case are distinguishable from *Hyatt*. According to M.P.E.P § 2164.08, a single means claim is one in which "a means recitation does not appear in combination with another recited element of means." In *Hyatt*, the Federal Circuit explained that a single means claims was "a claim drafted in 'means-plus-function' format yet reciting only a single element instead of a combination." *Hyatt*, at 713.

Neither claim 1 nor claim 18 of the present application fit either of these descriptions. Claims 1 and 18 are method claims requiring the use of cells comprising a G protein-coupled receptor that specifically binds to a polypeptide having the amino acid sequence of GASP SEQ ID NO:2 (GASP1) or GASP SEQ ID NO:6 (GASP2) in addition to requiring either an inhibitor or an enhancer

polypeptide. Furthermore, the enhancer polypeptide of claim 18 is defined in terms of amino acid sequence, as well as a recited property. By contrast, the claim at issue in *Hyatt* recited:

> A Fourier transform processor for generating Fourier transformed incremental output signals in response to incremental input signals, said Fourier transform processor *comprising* incremental *means for* incrementally generating the Fourier transformed incremental output signals in response to the incremental input signals.

Id. This claim differs from claims 1 and 18 of the present application in that the *Hyatt* claim recites a device, but recites no structure other than a single means. In effect, the *Hyatt* claim is an attempt to patent a desired result without limitation on the tangible means of achieving that result. Claims 1 and 18, on the other hand, recite multiple elements (specific cells and either an inhibitor or an enhancer polypeptide) and furthermore restrict certain elements to specific structures. Because claims 1 and 18 are not single means claims, and because the facts of the present case are distinguishable from those of *Hyatt*, Applicants respectfully submit that *Hyatt* does not support the enablement rejection.

The Examiner also relies on *Fiers v. Revel*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993). Applicants believe that this reliance is similarly misplaced. As the *Fiers* court expressly stated:

> The issue here . . . is conception of the DNA of the count, not enablement. Enablement concerns teaching one of ordinary skill in the art how to practice the claimed invention. . . . Since Fiers seeks to establish priority under section 102(g), the controlling issue here is whether he conceived a DNA coding for beta-IF, not whether his method was enabling.

Fiers, at 1605. Moreover, the count at issue in *Fiers* was analogous to the single means claim of *Hyatt* in that the *Fiers* count recited a "DNA which consists essentially of a DNA which codes for human fibroblast interferon-beta polypeptide." In other words, the *Fiers* count recited only one element that was defined in terms of a desired result. The claims at issue in the present case, by contrast, recite multiple elements that are defined structurally, as well as functionally.

It appears that, in applying *Hyatt* and *Fiers* to the facts of the present case, the Examiner has focused on the scope of the inhibitor recited in claim 1 and the scope of the enhancer polypeptide recited in claim 18. In the present case, claim 1 is directed to a method of inhibiting agonist-induced

down-regulation of GPCRs based on inhibiting binding between the GPCR and a GASP polypeptide. The specification includes a working example in which this interaction is inhibited with a dominant-negative fragment of GASP1 and indicates that a similar fragment of GASP2 could also be used. Applicants' specification, page 23, para. 0096. The specification also indicates that an expression vector including a polynucleotide encoding an inhibitory polypeptide can be administered to cells. Applicants' specification, page 24, para. 0098.

In light of this guidance, other methods of inhibiting the GPCR-GASP interaction would be readily apparent to those of skill in the art. For example, intrabodies are well known to those of skill in the art and could be employed to express antibody inhibitors within cells. More specifically, an intrabody is an intracellular antibody, in this case, capable of recognizing and binding to either the GPCR or GASP. The intrabody is expressed by an "antibody cassette" containing a polynucleotide encoding the portion of an antibody capable of binding to the target operably linked to a promoter that permits expression of the antibody in the cell(s) of interest. The construct encoding the intrabody is delivered to the cell where the antibody is expressed intracellularly and binds to the target (GPCR or GASP), thereby disrupting the GPCR-GASP interaction. The preparation of antibodies is routine, and the preparation of anti-GASP antibodies is described in the specification at pages 49-52. Recombinant techniques suitable for producing antibody cassettes are also well known and are described in the specification with respect to the recombinant production of GASP and DOR polypeptides at pages 40-44. Methods of making and delivering antibody cassettes for intrabody production were in use well before the priority date of the present application, as evidenced, for example, by U.S. Patent Nos. 6,072,036, 6,004,940, and 5,965,371.

In addition, the specification describes a number of screening methods that can be employed to identify other modulators of the GPCR-GASP interaction. For example, the specification teaches that prescreening for modulators can be carried out based on binding to GASP polypeptides or polynucleotides (pages 52-54). In one embodiment, the ability of a test agent to compete with GPCR binding to GASP is measured. Applicants' specification, page 53, para. 0186. As the specification indicates, analogous prescreening methods can be carried out based on binding to GPCR polypeptides (page 54). Additional screening methods, and details for carrying out the screening methods of the application, are described in the specification at pages 54-60. Accordingly, Applicants submit that the specification contains ample guidance in support of the inhibitor recited in claim 1.

Claim 18 is directed to a method of enhancing agonist-induced down-regulation of GPCRs based on administering a polypeptide having at least 70% amino acid sequence identity to GASP1 or GASP2. The Examiner acknowledges that "the specification has . . . provided sufficient guidance to use naturally occurring [GASP1 and 2]," but notes that the claims "require the use of a vast genus of amino acid sequence variants of the naturally occurring [GASP1 and 2]." Office Action, page 5.

As a threshold matter, Applicants respectfully point out that the claims do not "require" the use of the genus of polypeptides having at least 70% amino acid sequence identity to GASP1 or GASP2. Such use is within the scope of claim 18, but only one such polypeptide need be used to practice the invention.

In support of the rejection, the Examiner has cited journal articles indicating that it is difficult to predict how structural changes will affect protein function. This rationale assumes that to enable the use of amino acid sequence variants, it would be necessary to provide information in the specification that would allow one to predict which variants would have the desired function and thus avoid the need for **any** experimentation. However, such advance predictability is not required; **the need for some experimentation does not defeat enablement**. It is well settled that routine experimentation, such as, for example, screening hundreds of hybridomas to identify an antibody having the desired specificity, is not undue.

The Examiner contends that the determination of "the positions in the protein which are tolerant to change" represents undue experimentation. Office Action, page 5. However, the well-known technique of alanine scanning, for example, allows one of skill in the art to make this determination by generating variant polypeptides in which each successive amino acid is replaced with the amino acid alanine and subsequently tested for activity. In this case, such testing would entail a simple assay for binding to the GPCR of interest, such as are described in the specification. This experimentation is just as routine as, and no more laborious than, screening hybridomas for a desired binding activity.

However, the Examiner also asserts that the determination of "the nature and extent of changes that can be made in these positions" would also require undue experimentation. *Id.* at pages 5-6. This assertion ignores the availability of techniques such as phage display whereby every possible amino acid substitution at multiple positions can be varied simultaneously and screened in pools,

allowing the selection of those variants having a desired binding affinity. Such techniques make it possible to analyze very large numbers of amino acid sequence variants with a few rounds of binding and selection. This experimentation is merely routine and is widely used to produce amino acid variants of a polypeptide that retain a desired binding activity. Both alanine scanning and phage display were available at least a decade before the priority date of the present application. Accordingly, Applicants submit that the specification clearly enables one skilled in the art to identify amino acid sequence variants of GASP1 and 2 that can be employed as enhance polypeptides as recited in claim 18.

But more to the point is that the Examiner has overlooked the fact that the claim are not directed to these agents per se, but to methods that recite additional elements. The Examiner is reminded that it is well-established law that an enablement rejection **must be directed to the patentable or inventive principles** of the claimed method. *See, e.g., In re Fuetterer*, 319 F.2d 259, 265 USPQ 217 (CCPA 1963); *Application of Herschler*, 591 F.2d 193, 200 USPQ 711 (CCPA 1979). In the present case, the inventive principle is based on the discovery that the GPCR-GASP interaction mediates agonist-induced down-regulation of GPCRs. Those of skill in the art can practice the methods of modulating this interaction that are recited in claim 1 and 18 even though Applicants have not described every potential technique for carrying out this modulation.

The situation is analogous to that described in *Application of Fuetterer*, 138 USPQ 217 (CCPA 1963). In *Fuetterer,* the applicant invented a novel rubber stock composition that included "an inorganic salt capable" of acting as a colloid-suspending agent. The Examiner argued that the amount of experimentation required to successfully use undisclosed inorganic salts was undue and required the applicant to restrict his claims to specific salts disclosed. The CCPA reversed the Examiner's rejection, explaining that the invention was not the salt, but the combination of inorganic salts with the other elements of the claim. The fact that undisclosed inorganic salts might be later discovered did not preclude broad claims to the **inventive combination**.

Fuetterer was followed by *Application of Herschler*, 200 USPQ 711 (CCPA 1979). In *Herschler*, the applicant had discovered that DMSO was useful as a transdermal carrier for physiologically active steroids. The CCPA found that a priority application describing the use of DMSO to transport a particular steroid supported a claim to a method of transporting the genus of all steroids. Citing *Fuetterer*, the court explained that Herschler's claims were drawn to a method of

administration of steroids and not to administration of a particular steroid compound. The court noted that **the inventive principle was directed to the method, and that the exemplification using specific steroids was not the point of patentability**.

In *Fuetterer*, the invention was the combination of salts with other compounds, thus the teaching of particular salts was not a proper focus of the enablement inquiry. Similarly, in *Herschler*, the invention was a method of transporting steroids, therefore the teaching of particular steroids was not a proper focus of the enablement inquiry. In the present case, the invention is the recognition that modulation of the GPCR-GASP interaction modulates agonist-induced downregulation of GPCRs. Accordingly, the teaching of every possible method of modulating this interaction is not properly the focus of enablement inquiry.

Moreover, to confine Applicants to specifically exemplified modulators effectively denies Applicants the benefit of their invention. Requiring Applicants to expressly identify **every** possible method of modulating GPCR-GASP interaction to obtain meaningful protection imposes an undue burden. Conversely, limiting the protection for Applicants' invention to the specifically exemplified modulators renders the invention easy to "design around," as a competitor seeking to avoid infringement would merely have to routinely screen and identify additional other modulators. As stated by the CCPA:

> To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

In re Goffe, 542 F.2d 564, 191 USPQ 429, 431 (CCPA 1976). In *Goffe*, the court held that applicants were not to be limited to the single "agglomerable material" disclosed when other suitable materials could be determined without undue experimentation. Here, Applicants should not be limited to the specifically exemplified modulators when others can be identified without undue experimentation.

The Examiner also objects that "no specific teachings are provided to accomplish any particular method *in vivo*, and asserts that the general discussion in the application of *in vivo* administration of modulators is insufficient. Office Action, page 4. Applicants respectfully submit that this position is contrary to well-settled precedent. The courts have consistently held that "[n]ot every last detail [of an invention need] be described [in a patent specification], else patent

specifications would turn into production specifications, which they were never intended to be." *In re Gay*, 309 F.2d 769, 774 (CCPA 1962). Citing this decision, the Board of Patent Appeals and Interferences has more recently echoed this point in its statement that "the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 U.S.C. 112, first paragraph." *Staehelin v. Secher*, 24 USPQ2d 1513, 1516 (Bd. Pat. App. & Int. 1992).

In re Cook exemplifies the proper § 112 analysis of claims rejected under the first paragraph on facts similar to those in the present case. In *Cook*, the invention related to a zoom lens. *In re* Cook, 439 F.2d 730, 169 USPQ 298 (1971). The inventors had discovered that maintaining certain relationships among a relatively small number of parameters extended the range over which the scale of the image provided by the lens assembly could be varied without unacceptable distortion. *Id.* at 731. These relationships were set forth in the rejected claims, and the specification contained six examples of lens assemblies. On this record, the court reversed the § 112 rejections, holding:

> **Appellants do not purport to have solved all of the time-consuming problems involved in the design of a new lens**; indeed, to the extent that their relationships add new calculations to the design of zoom lenses, they may even have increased the time required. **What they do claim to have done is to have discovered a simple set of relationships** among some of the fundamental parameters involved in the design of zoom lenses which, if respected, will result in zoom lens assemblies which will be capable of zooming through a wider range than previous zoom lenses without experiencing an unacceptably high degree of image distortion at any point in their ranges of equivalent focal length variation. **They are thus, it seems to us, somewhat in the position of a suspension-bridge builder who has discovered that maintaining certain relationships between the height above the roadway of the main piers and the distance between the piers will result in bridges of substantially increased strength. Disclosure by the bridge builder of this relationship would certainly not solve all the time-consuming problems of bridge designing or building, but it would, we think, enable any person skilled in the art to practice the invention.** Similarly, we feel that, while appellants' disclosure has not taught those skilled in the art how to design an entire new zoom lens in short order, it has taught those skilled in the art how to design a new zoom lens of the type here claimed without undue effort. The rejection therefore cannot be sustained on this rationale.

Id. at 732-33 (emphasis added). Similarly, in the present case, Applicants have discovered and claimed methods based on a new relationship: the link between GPCR-GASP interaction and agonist-induced down-regulation of the GPCR. The disclosure of this relationship, along with multiple ways of modulating the GPCR-GASP interaction enables any person skilled in the art to practice the invention. The practice of the claimed methods with modulators other than those exemplified in the specification could require some expenditure of effort, as is the case for zoom lens or bridge design. However, as *Cook* makes clear, such effort is not undue when what the applicants claim to have discovered is a relationship(s) that facilitates designing a zoom lens or bridge or, as here, modulating agonist-induced down-regulation.

Thus, the specification fully enables the only pending independent claims, claims 1 and 18. The Examiner has cited no separate basis for the enablement rejection of any of the pending dependent claims. Accordingly, Applicants respectfully request withdrawal of the § 112, first paragraph rejection.

Conclusion.

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

Any required fees accompany this response; if the amount of such fees is incorrect, please charge any required fees, or credit any overpayments, to Deposit Account No. 500388 (Order No. EGCRP010US).

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 267-4160.

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